NEW ZEALAND DATA SHEET

VACLOVIR®

1. Product Name

Vaclovir 500 mg & 1000 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 500 mg or 1000 mg of valaciclovir (as hydrochloride). For

the full list of excipients, see section 6.1.

3. Pharmaceutical Form

VACLOVIR 500 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir.

VACLOVIR 1000 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 1000 mg valaciclovir.

VACLOVIR 500 mg and VACLOVIR 1000 mg tablets can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

VACLOVIR is indicated for the treatment of herpes zoster (shingles) and the reduction of zoster – associated pain, which includes acute and post herpetic neuralgia, when given to immunocompetent patients in infection of less than 72 hours duration.

VACLOVIR is indicated for the treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes in immunocompetent patients.

VACLOVIR can prevent lesion development when taken at the first signs and symptoms of a herpes simplex virus (HSV) recurrence.

VACLOVIR is indicated for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes in immunocompetent and immunocompromised patients.

VACLOVIR is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation. CMV prophylaxis with VACLOVIR reduces acute graft rejection (renal transplant patients), opportunistic infections and other herpes virus infections (herpes simplex virus (HSV), varicella zoster virus (VZV)).

4.2 Dose and method of administration

Dose

Treatment of varicella zoster virus infections

Herpes zoster (shingles) including ophthalmic zoster

The dosage in adults is 1000 mg of VACLOVIR to be taken 3 times daily for 7 days.

Treatment of herpes simplex infections

The dosage in adults is 500 mg of VACLOVIR to be taken twice daily.

For recurrent episodes, treatment should be for 5 days. For initial episodes, which can be more severe, treatment may have to be extended to 10 days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately the first signs or symptoms appear.

Prevention (suppression) of recurrences of herpes simplex infections

In immunocompetent adult patients, 500 mg of VACLOVIR to be taken once daily.

Some patients with very frequent recurrences (e.g. 10 or more per year) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily).

For immunocompromised adult patients the dose is 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease

Dosage in adults and adolescents (from 12 years of age)

The dosage of VACLOVIR is 2 g four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance.

The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.

Special populations

Elderly

Dosage modification is not required unless renal function is significantly impaired. Adequate hydration should be maintained.

Renal impairment

Herpes zoster treatment and herpes simplex treatment and prevention (suppression)

Caution is advised when administering VACLOVIR to patients with impaired renal function. Adequate hydration should be maintained.

The dosage of VACLOVIR should be reduced in patients with significantly impaired renal function as shown in the table below.

There is no experience with valaciclovir use in paediatric patients with a creatinine clearance of <50 mL/min/1.73m^2.

Indication	**Creatinine clearance mL/min**	**VACLOVIR dosage**
Herpes zoster (treatment) in immunocompetent patients	at least 50 30 to 49	1 g three times a day 1 g twice a day

	10-29 less than 10	1 g once a day 500 mg once a day
Herpes simplex (treatment) in immunocompetent patients	at least 30 less than 30	500 mg twice a day 500 mg once a day
Herpes simplex prevention (suppression): - immunocompetent patients - immunocompromised patients	 at least 30 less than 30 at least 30 less than 30	 500 mg once a day 250 mg once a day 500 mg twice a day 500 mg once a day

In patients on intermittent haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

CMV prophylaxis

Caution is advised when administering VACLOVIR to patients with impaired renal function. Adequate hydration should be maintained.

The dosage of VACLOVIR should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine clearance mL/min	**VACLOVIR dosage**
75 or greater	2 g four times daily
50 to less than 75	1.5 g four times a day
25 to less than 50	1.5 g three times a day
10 to less than 25	1.5 g twice a day
less than 10 or dialysis◊	1.5 g once a day

◊In patients on haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment. The VACLOVIR dosage should be adjusted accordingly.

Hepatic impairment

Studies with a 1 g unit dose of valaciclovir show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment; however, clinical experience is limited. For higher doses recommended for CMV prophylaxis (see section 4.4).

Paediatric

There are no data available on the use of valaciclovir in children.

4.3 Contraindications

VACLOVIR is contra-indicated in patients known to be hypersensitive to valaciclovir, aciclovir or any components of the formulations of VACLOVIR.

4.4 Special warnings and precautions for use

Thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease who were treated with valaciclovir for prolonged periods and also in allogenic bone marrow transplant and renal transplant recipients who were treated with valaciclovir while participating in clinical trials at doses of 8 grams per day. Treatment with valaciclovir should be stopped immediately if clinical signs, symptoms, and laboratory abnormalities consistent with TTP/HUS occur.

Similar signs have been observed in patients with the same underlying or concurrent conditions who were not treated with valaciclovir.

Use of valaciclovir at doses of 1000 mg/day in immunocompromised patients with $CD4^+$ counts > $100x10^6$L has not been associated with occurrences of thrombotic microangiopathy (TMA). However use in severely immunocompromised patients ($CD4^+$ counts < $100x10^6$ L) has not been examined at this low dosage.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS, which can be life-threatening or fatal, has been reported in association with valaciclovir treatment. At the time of prescribing patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patients has developed DRESS with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time.

Hydration status

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Patients without adequate hydration: Precipitation of aciclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Use in renal impairment and in elderly patients

Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Use of high dose valaciclovir in hepatic impairment and liver transplantation

There are no data available on the use of high doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg to these patients (see section 4.4 – Use in hepatic impairment).

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Use in genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. Continuous therapy with valaciclovir in patients with recurrent genital herpes reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminated the risk of transmission. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible, Therefore, in addition to therapy with valaciclovir, It is recommended patients use safer sex practices. As genital herpes is a sexually transmitted infection, patients should, in order to further reduce the risk of infecting partners, avoid contact with lesions, damaged skin/mucosa, and avoid intercourse when lesions and/or symptoms are present. Genital herpes is frequently transmitted in the absence of symptoms through asymptomatic viral shedding; therefore patients should be counselled to use safer sex practices. The effect of valaciclovir on transmission of sexually transmitted infections other than herpes (including HIV, gonorrhoea, syphilis and Chlamydia) is unknown.

The efficacy of valaciclovir in reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples and couples not counselled to use safer sex practices.

Use in ocular HSV infections

Clinical response should be closely monitored in these patients. Considerations should be given to intravenous antiviral therapy when response to oral therapy is unlikely to be sufficient.

Use in CMV infections

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that valaciclovir should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).

Central nervous system effects

Reversible neurological reactions including agitation, dizziness, confusion, hallucinations, rarely decreased consciousness and very rarely tremor, ataxia, dysarthria, convulsions, encephalopathy and coma have been reported. These events are usually seen in patients with renal impairment or with other predisposing factors. In organ transplant patients receiving high doses (8g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses. Valaciclovir should be discontinued if central nervous system adverse reactions occur.

Use in hepatic impairment

For further information see section 5.2.

Use in renal impairment

Renal insufficiency or acute renal failure has been observed in patients taking valaciclovir at the recommended dosage and/or with no previous renal conditions and may be associated with renal

pain.

The dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Valaciclovir is converted to aciclovir which is eliminated by renal clearance (see section 5.2). Patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Cases of acute renal failure have been reported in patients without adequate hydration. Precipitation of aciclovir in renal tubules may occur when the solubility is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Caution should be exercised when administering valaciclovir with significant renal impairment or those receiving potentially nephrotoxic agents, since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system such as those that occur infrequently in patients treated with intravenous aciclovir.

Use in the elderly

Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Elderly patients are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Paediatric use

Safety and effectiveness in children have not been established.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines (including e.g. tenofovir) administered concurrently that compete with this mechanism or inhibit active tubular secretion may increase aciclovir plasma concentrations by this mechanism following valaciclovir administration. Similarly, valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

Following 1 g valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism by about 45%, and reduce aciclovir renal clearance by about 25%, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65%. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

In patients receiving high-dose valaciclovir (8 g/day) (e.g., at doses for zoster treatment or CMV prophylaxis) caution is required during concurrent administration with medicines which inhibit active renal tubular secretion, compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited experience with the use of combination of valaciclovir

and mycophenolate mofetil.

Care is also required (with monitoring for changes in renal function) if administering high-dose valaciclovir with medicines which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of valaciclovir in pregnant women. A prospective epidemiologic registry of aciclovir use during pregnancy has been ongoing since June 1984.

Pregnancy registries have documented the pregnancy outcomes in women exposed to valaciclovir or to any formulation (oral or intravenous) of aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered and post marketing experience indicate no malformative or foeto/neonatal toxicity. Registry findings do not indicate an increased risk of major birth defects after aciclovir exposure in comparison with the general population. The accumulated case histories represent an insufficient sample for reaching reliable and definitive conclusions regarding the risk associated with aciclovir exposure during pregnancy. The daily aciclovir AUCs (area under plasma concentration-time curve) following valaciclovir 1000mg and 8000mg daily would be approximately 2 and 9 times greater than that expected with oral aciclovir 1000 mg daily, respectively. Animal studies do not show reproductive toxicity for valaciclovir (see section 5.3)

There are limited data on the use of valaciclovir in pregnancy. valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Breastfeeding

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. In a study conducted on 5 women, following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal aciclovir serum concentrations. The aciclovir AUC was 2.2 times (range 1.4 to 2.6) higher in breast milk compared to maternal serum.

In other studies, conducted with oral aciclovir administration, aciclovir had been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding aciclovir plasma concentration.

Caution is therefore advised if valaciclovir is to be administered to a breastfeeding mother. Valaciclovir should only be administered to breastfeeding mothers if the benefits to the mother outweigh the potential risks to the baby.

Fertility

No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 aciclovir recipients, with culture confirmed genital HSV-2 and with normal baseline sperm counts after 6 months of daily treatment with 400 mg to 1 g aciclovir.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of valaciclovir should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of valaciclovir on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Valaciclovir was well tolerated when used for the treatment of herpes zoster and genital herpes in clinical trials. The most commonly reported adverse experiences were headache and nausea and

these were reported in a similar proportion of patients on valaciclovir, aciclovir and placebo.

More serious ARs such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure, neurological disorders and DRESS (see section 4.4) are discussed in greater detail in other sections of the data sheet.

Herpes Zoster infection

The following table lists all adverse events reported during a six month observation period in immunocompetent patients receiving short-term treatment (7 or 14 days) with valaciclovir and reference products in controlled clinical trials.

	% Incidence of adverse events			
Patient age group	**≥ 50 years**		**18 to 50 years**	
	Valaciclovir 1 g 3 x daily (n=765) 14 days n=381 7 days n=384	**Aciclovir 800 mg 5 x daily 7 days (n=376)**	**Valaciclovir 1 g 3 x daily 7 days (n=202)**	**Placebo 7 days (n=197)**
Nausea	16.5	19.1	9.9	7.6
Headache	12.9	12.8	16.8	11.7
Vomiting	6.8	7.7	4.5	2.5
Diarrhoea	5.5	7.4	4.5	6.1
Constipation	5.1	5.3	1.5	2.5
Asthenia	4.4	5.3	3.0	3.6
Dizziness	3.7	5.9	2.0	2.0
Abdominal Pain	3.3	2.7	2.5	1.5
Anorexia	3.0	2.7	0.5	2.0
Dyspepsia	2.5	1.9	-	-
Dry mouth	1.8	0.5	-	-
Flatulence	1.8	1.6	-	-
Fever	1.4	2.4	-	-
Insomnia	1.6	0.5	-	-
Rhinitis	1.3	1.6	1.5	1.5
Chills	1.0	1.6	-	-
Back Pain	1.0	0.5	-	-
Nervousness	1.0	0.0	-	-
Somnolence	0.9	2.1	-	-
Pain	0.8	1.6	-	-
Rash	0.7	1.9	-	-
Myalgia	-	-	0.5	2.5
Infection	-	-	2.0	1.0

HSV infections:

Initial and recurrent genital herpes (short term treatment):

The adverse events reported by greater than 2% of a given treatment group in the initial and recurrent genital herpes clinical trials with valaciclovir and reference products used in the trials are listed in the table below.

Patient age group	**% Incidence of adverse events 17 – 79 years**		
	Valaciclovir 1g 2 x daily (n=1203) 10 days n = 323 5 days n = 880	**Aciclovir 200 mg 5 x daily 5 days (n=1187)**	**Placebo (n=441)**

	500 mg 2 x daily		
Headache	16	11	14
Nausea	6	7	7
Diarrhoea	4	3	6
Dizziness	3	2	2
Abdominal pain	2	3	2
Asthenia	2	2	4
Rhinitis	2	2	2
Pharyngitis	1	2	1
Pain	1	1	2
Dyspepsia	1	1	2
Vomiting	1	2	0
Back pain	1	1	2

Prevention of genital herpes (long-term preventative therapy):

The adverse events reported at an incidence of 5% or greater in a given treatment group, in clinical trials for the preventative treatment of genital herpes with valaciclovir and reference products, are listed below.

	% Incidence of adverse events					
	Immunocompetent				**Immunocompromised**	
	V 500mg 1 x daily 52 weeks N=266	**V 250mg 2 x daily 52 weeks N=274**	**A 400mg 2 x daily 52 weeks N=267**	**PBO 52 weeks N=134**	**V 500mg 2 x daily 48 weeks N=355**	**A 400mg 2 x daily 48 weeks N=349**
Headache	38	35	37	34	18	17
Rhinitis	23	26	25	18	13	14
Infection	18	15	21	16	16	13
Flu syndrome	12	20	18	13	7	7
Pharyngitis	12	8	11	14	11	13
Nausea	11	9	12	8	16	12
Back Pain	8	12	13	6	6	7
Diarrhoea	9	8	12	14	19	19
Abdominal Pain	9	9	7	6	12	7
Pain	11	6	8	4	6	6
Sinusitis	8	7	12	5	7	7
Accidental Injury	7	7	10	3	3	5
Dysmenorrhoea	5	8	8	4	-	-
Dyspepsia	3	6	7	8	3	4
Rash	5	5	6	7	14	14
Arthralgia	5	5	7	4	3	3
Depression	5	5	4	5	9	7
Allergic Reaction	6	6	4	4	-	-
Urinary Tract Infection	5	2	7	2	-	-
Bronchitis	5	4	5	2	3	7
Myalgia	5	4	8	2	3	5
Asthenia	4	5	3	5	8	9
Tooth Disorder	5	3	4	3	1	3
Unevaluable Reaction	5	3	5	2	3	4
Migraine	4	4	5	2	-	-
Acne	3	4	3	3	5	3

Dizziness	2	5	3	1	2	3
Insomnia	5	3	1	2	3	4
Vomiting	3	3	5	2	7	5
Pruritus	2	3	2	1	5	3
Increased Coughing	3	4	1	2	6	10
Fever	3	1	1	1	11	11
Rectal Disorder	-	-	-	-	4	5

V = Valaciclovir
A = Aciclovir
PBO = Placebo

Prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation.

Valaciclovir was well tolerated in the clinical studies of renal and heart transplant patients. The nature and frequency of adverse events were similar between placebo, aciclovir and valaciclovir treated patients, with the exception of adverse events relating to the CNS (hallucination, confusion and thinking abnormality). These were reported more frequently in valaciclovir than placebo in renal transplant patients. The most common adverse events reported in the renal transplant patients were anaemia, hypertension and headache. Headache and myalgia were the most common adverse events reported in the heart transplant patients. All the clinical adverse events occurring at an incidence of ≥ 5% or ≥ 20% in a given treatment group, in clinical trials for CMV prophylaxis following renal and heart transplants respectively are listed in the tables below.

Summary of all adverse events reported at an incidence ≥ 5% by renal transplant recipients in clinical trials for CMV prophylaxis		
	Renal transplant recipients	
Adverse Event	**Valaciclovir* (n = 306)**	**Placebo (n = 310)**
Anaemia	12%	12%
Hypertension	11%	8%
Headache	9%	11%
Diarrhoea	9%	12%
Abdominal Pain	8%	11%
Leukopenia	8%	8%
Hallucination	8%	1%
Fever	8%	11%
Nausea	8%	7%
Vomiting	8%	7%
Peripheral Oedema	8%	9%
Confusion	7%	2%
Dyspnoea	7%	5%
Pain	7%	7%
Constipation	7%	5%
Insomnia	6%	3%
ALT** increase	5%	6%
Thrombocytopenia	5%	5%
Pruritus	5%	2%
Arthralgia	5%	6%

Tremor	4%	6%
Oedema	4%	5%
AST*** increase	4%	6%

Summary of all adverse events reported at an incidence ≥ 20% by heart transplant recipients in clinical trials for CMV prophylaxis.		
	Heart transplant recipients	
Adverse Event	**Valaciclovir* (n = 14)**	**Aciclovir (n = 13)**
Headache	57%	62%
Myalgia	57%	46%
Cough increase	57%	46%
Peripheral Oedema	50%	62%
Asthenia	43%	15%
Effus Pericard	43%	46%
Pain	43%	31%
Dyspnoea	36%	38%
Back Pain	29%	15%
Nausea	21%	23%
Insomnia	21%	15%
General Oedema	21%	54%
Hypertension	21%	38%
Somnolence	21%	23%
Constipation	21%	15%
Depression	21%	15%
Sleep Disorder	21%	15%
Chest Pain	21%	-
Dizziness	7%	31%
Diarrhoea	7%	23%
Mouth Ulcer	-	23%

* The dosage adjustment of valaciclovir (and aciclovir) in the renal and heart transplant clinical studies differed.

** ALT = alanine aminotransferase.

*** AST = aspartate aminotransferase.

Post-marketing data

The following adverse events have been observed during post-approval use of valaciclovir:

Blood and lymphatic system disorders

Leukopenia*, thrombocytopenia, thrombotic microangiopathy (TMA) (refer to section 4.4).

*Leukopenia is mainly reported in immunocompromised patients.

Aplastic anaemia, leukocytoclastic vasculitis, thrombotic thrombocytopenic purpura / hemolytic uremic syndrome (TTP/HUS).

Immune system disorders

Anaphylaxis

Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash and uticaria.

Psychiatric and nervous system disorders

Headache, dizziness, confusion, hallucinations, decreased consciousness, agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma, aggressive behaviour, delirium.

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8000 mg daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders

Dyspnoea

Gastrointestinal disorders

Abdominal discomfort, vomiting, diarrhoea, nausea

Hepato-biliary disorders

Reversible increases in liver function tests (e.g. bilirubin, liver enzymes), occasionally described as

hepatitis.

Skin and subcutaneous tissue disorders

Rashes including photosensitivity, pruritus, urticaria, angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiform (see section 4.4).

Renal and urinary disorders

Renal pain, haematuria (often associated with other renal events), renal impairment, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended dose), tubulointerstitial nephritis.

Renal pain may be associated with renal failure.

Intratubular precipitation of aciclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see section 4.4). Elevated blood creatin and blood urea nitrogen (BUN).

General

Facial edema, hypertension, tachycardia

Ophthalmologic

Visual abnormalities

Other

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms and signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, ATC code: J05AB11

Mechanism of action

Valaciclovir is rapidly and almost completely converted in man to aciclovir probably by the enzyme valaciclovir hydrolase. Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2 (IC50 0.1 – 3.0μM), varicella-zoster virus (VZV) (IC50 1.6 – 5.1μM) and human cytomegalovirus (HCMV) (IC50 10 - 200μM). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form. The first stage of phosphorylation requires the activity of a virus-specific enzyme: thymidine kinase in HSV and VZV infected cells or protein kinase in HCMV infected cells. This requirement for activation of aciclovir by a virus specific enzyme largely explains its unique selectivity. The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype. In animal models, the viral fitness and pathogenicity of this phenotype appears to be reduced. Infrequently, reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants in animal models resembles that of the wild-type virus.

Resistance of HSV and VZV to aciclovir occurs by the same mechanisms. While most of the aciclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valaciclovir (and therefore, to aciclovir) should be considered in patients who show poor clinical response during therapy.

Clinical trials

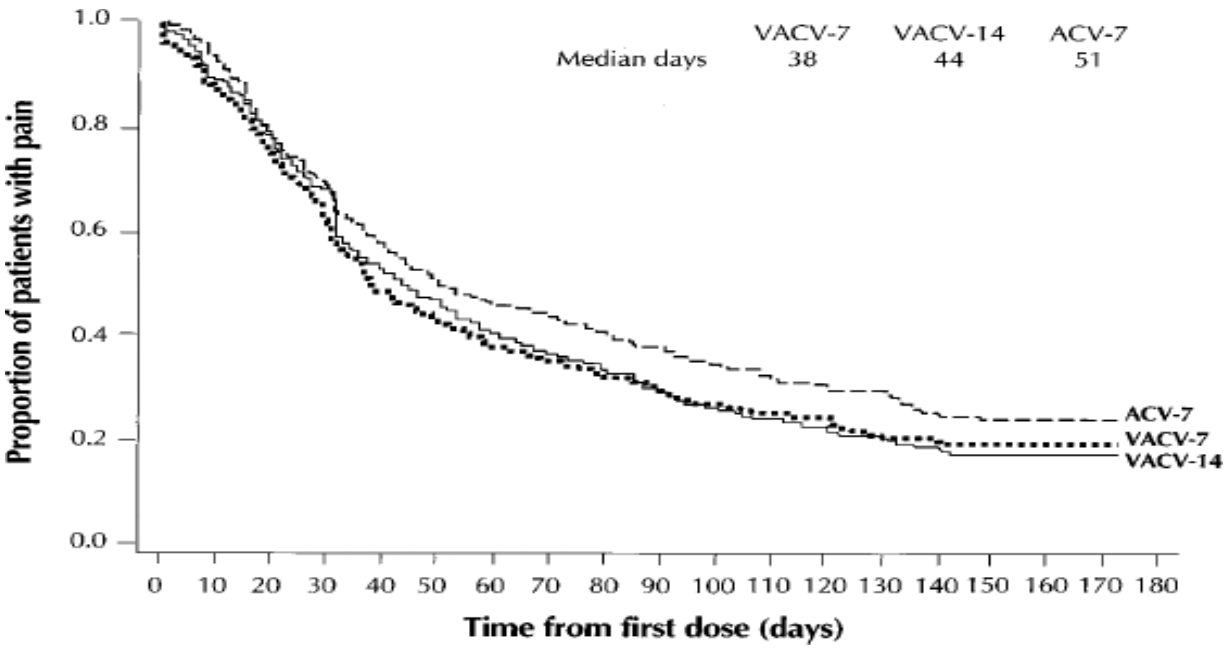
Herpes zoster infections:

Two doses of valaciclovir were compared to aciclovir in a double blind randomised trial in immunocompetent patients aged 50 years and over with herpes zoster (n=1141). All patients were treated within 72 hours of the appearance of rash. Valaciclovir 1 g three times daily for seven days achieved statistically significant reductions in the duration of zoster-associated pain (which is the sum of acute pain and post-herpetic neuralgia) and in the duration of post-herpetic neuralgia when compared with aciclovir. There was no statistically significant differences between the three treatments for the resolution of rash. See table below.

	Median duration (days)		
	valaciclovir		aciclovir
	1 g three times daily		800 mg five times daily
	for 7 days (n=384)	for 14 days (n=381)	for 7 days (n=376)
All Zoster associated Pain (Z-aP)	38	44	51
Post Herpetic Neuralgia (PHN)	30	35	39

There was no significant difference to the duration of zoster-associated pain when treatment was started within 48 hours or 72 hours. Patients treated within 48 hours of rash onset were found to have faster healing rates as measured by the duration of new lesion formation and time to crusting or healing of 50% or more of lesions. Thus, greater benefit is gained if the drug is started within 48 hours. See figure below.

Duration of zoster-associated pain: Kaplan-Meier plots for valaciclovir versus aciclovir for patients ≥ 50 years old



Note: ACV-7 – aciclovir at 800mg five times daily for 7 days; VACV-7 – valaciclovir at 1000mg three times daily for 7 days; VACV-14 – valaciclovir at 1000mg three times daily for 14 days.

In the second, placebo controlled trial in patients under 50 years of age (n=399), demonstration of efficacy was restricted to a small decrease in mean time to cessation of new lesion formation. No significant effects were demonstrated for other outcomes of herpes zoster in this age group. Nevertheless, the occasional younger patients with severe herpes zoster may benefit from therapy with valaciclovir. Herpes zoster is usually a milder condition in younger patients.

In ophthalmic zoster oral aciclovir has been shown to reduce the incidence of stromal keratitis and

both the incidence and severity of anterior uveitis but not other ocular complications or acute pain. The recommended dose of valaciclovir produces higher plasma concentrations of aciclovir than those associated with these beneficial effects.

Acute treatment of Initial and Recurrent Herpes Simplex Virus (HSV) Infections:

Four large multicentre, randomised double-blind trials were conducted in adults with herpes simplex infections. These studies included a total of 3569 treated patients of whom 1941 received valaciclovir.

Initial genital herpes simplex infections:

One study compared valaciclovir (1000 mg twice daily) with aciclovir (200 mg five times daily) administered for 10 days in immunocompetent patients with initial (primary or first episode) genital herpes. Patients reported to the clinic for treatment within 72 hours of the first signs or symptoms of genital herpes.

Patients were randomized to receive valaciclovir (n=323) or Zovirax (n=320) for 10 days. The median time to lesion healing was 9 days in each treatment group. The median time to the cessation of viral shedding was 3 days in each treatment group. Median time to cessation of pain was 5 days in each treatment group.

Recurrent genital herpes simplex infections:

The other three studies enrolled immunocompetent patients with a history of recurrent genital herpes infections. These studies compared valaciclovir (1000 mg and/or 500 mg twice daily) with aciclovir (200 mg five times daily) and/or placebo, administered for 5 days. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

The primary efficacy end-points in each study were:

- lesions healing time and pain/discomfort.
- proportions of patients in whom lesions were prevented (aborted lesions).
- viral shedding.

In one study, patients were randomized to receive five days of treatment with either valaciclovir 500 mg bid (n=360) or placebo (n=259). **Duration of lesions**: The median time to lesion healing was four days in the group receiving valaciclovir 500 mg versus six days in the placebo group. **Cessation of viral shedding:** The median time to cessation of viral shedding in patients with at least one positive culture (42 % of the overall study population) was two days in the group receiving valaciclovir 500 mg versus four days in the placebo group. **Cessation of pain:** The median time to cessation of pain was three days in the group receiving valaciclovir 500 mg versus four days in the placebo group. Results supporting efficacy were replicated in the other two studies. **Prevention of lesion development (Aborted episodes):** Pooled analysis of the three studies also showed that the use of valaciclovir in patients who self-initiated treatment in the prodrome, increased the chances of preventing lesion development (aborting episodes) by 31% to 44 % compared with placebo.

Prevention of Recurrent genital herpes simplex virus (HSV) infection:

Three large, multicentre, double-blind, randomised trials were conducted to investigate the efficacy of valaciclovir for the prevention of recurrent genital HSV infection. Two studies evaluated the disease in immunocompetent individuals, while the third evaluated an immunocompromised (HIV-infected) population.

Immunocompetent patients:

The two trials conducted in immunocompetent patients included a total of 1861 patients, of which 1366 received valaciclovir for up to 52 weeks. The primary endpoint in both trials was defined as the first clinical recurrence of HSV infection, and the proportion recurrence free at the end of 12 months

was another endpoint. In Study BQRT/95/0026, 500mg once daily treatment with valaciclovir was compared with placebo in patients with a history of at least 8 recurrences per year. Clinical recurrence was defined as lesions reaching the papule/vesicle stage, and valaciclovir delayed or prevented 85% of the recurrences compared with placebo.

BQRT/96/0001 was a double blind study comparing a variety of valaciclovir doses and aciclovir with placebo. Clinical recurrence was defined as lesions at the macule/papule stage. As HSV infection had been identified as a strong prognostic factor in previous genital herpes studies, subgroup analyses was conducted according to recurrence history. The results from the proportional hazards analyses (hazard ratios and 95% CI) for the active treatment comparisons with placebo obtained within each subgroup are presented in table below.

HSV Recurrence Frequency	**Comparison**	**Hazard Ratio**	**95% Confidence Interval**
<10	VACV 250mg bd *vs* PBO	0.122	(0.083, 0.181)
	VACV 1000mg od *vs* PBO	0.160	(0.110, 0.231)
	VACV 500mg od *vs* PBO	0.182	(0.128, 0.258)
	VACV 250mg od *vs* PBO	0.319	(0.227, 0.448)
	ACV 400mg bd *vs* PBO	0.160	(0.109, 0.234)
≥10	VACV 250mg bd *vs* PBO	0.325	(0.226, 0.468)
	VACV 1000mg od *vs* PBO	0.274	(0.188, 0.400)
	VACV 500mg od *vs* PBO	0.451	(0.308, 0.659)
	VACV 250mg od *vs* PBO	0.632	(0.446, 0.895)
	ACV 400mg bd *vs* PBO	0.261	(0.181, 0.378)

Results show that 250mg twice daily offered the best clinical efficacy for suppression of genital herpes recurrences in this group of patients. However, the same total daily dose given as single daily dose (i.e. 500mg once daily) was also very effective, as confirmed with Study BQRT/95/0026.

Although 1000mg daily was more effective than 500mg once daily in the first study, the marginal difference between the two did not justify long term exposure to double the daily dose. The hazard ratio comparing valaciclovir 1000mg once daily and 500mg once daily indicated an increase in efficacy of only approximately 12% (hazard ratio 0.879, 95% CI 0.637, 1.211).

Immunocompromised patients:

A third study examined a total of 1062 immunocompromised patients (HIV-infected, CD^+ counts of ≥ 100/mm^3 at enrolment) of whom 713 received valaciclovir (1000 mg once daily, 500mg twice daily, 48 weeks) compared with 349 patients who received aciclovir (400 mg twice daily, 48 weeks). The primary endpoint was the time to first HSV recurrence (onset of macules/papules). The study demonstrated that valaciclovir 500 mg twice daily is as effective as aciclovir in preventing or delaying HSV infections in immunocompromised patients. Valaciclovir 500 mg twice daily was significantly more efficacious than valaciclovir 1000 mg once daily.

Reduction of Genital Herpes Simplex Virus transmission:

Study HS2AB3009 was a randomised, double blind, placebo controlled trial evaluating valaciclovir 500mg once daily for eight months in the prevention of HSV-2 transmission in heterosexual monogamous couples. 1484 couples received treatment with 741 source partners receiving placebo and 743 source partners receiving valaciclovir. Source partners had to be seropositive for HSV-2 and have a history of recurrent genital herpes with less than 10 recurrences per year. Susceptible partners could not be seropositive for HSV-2, but could be seropositive for HSV-1. Couples were encouraged to practice safer sex (including use of condoms). The primary endpoint of the study was the proportion of couples that developed clinical evidence of a first episode of genital herpes HSV-2 in the susceptible partner. Clinical evidence of a first episode was defined as symptomatic genital herpes confirmed by laboratory analysis.

The results of this study established that the proportion of couples with clinical symptoms of genital

herpes in the susceptible partner was higher in the placebo group than in the valaciclovir group (2.2% vs. 0.5% respectively). The risk of transmission of symptomatic genital herpes was reduced by 75% (95% CI 26%, 92%, p=0.011) in the valaciclovir group, a difference which is both clinically and statistically significant.

The results of the time to event analysis confirm those of the primary endpoint, with the time to clinical symptoms being significantly longer in the valaciclovir group compared with the placebo group (p=0.008).

The proportion of couples with overall acquisition* of genital HSV-2 infection in the susceptible partner was 3.6% (27/741) in the placebo group and 1.9% (14/743) in the valaciclovir group (p=0.054, approximate relative risk (95% CI): 0.52 (0.27, 0.97). These analyses show that there was a 48% reduction in the risk of acquiring HSV-2 infection in the valaciclovir group compared with the placebo group. This difference approached statistical significance for overall acquisition.

(* Overall Acquisition: in which the susceptible partner acquired genital herpes HSV-2 infection, as documented by HSV-2 seroconversion only, or by seroconversion and/or detection of the virus by culture or PCR, and irrespective of the presence of clinical symptoms).

The result of the analysis of time to overall acquisition of HSV-2 (Hazard Ratio: 0.52; 95% CI: 0.27, 0.99), which explicitly allows for differential length of follow-up, is statistically significant (p=0.039).

The proportion of couples with HSV-2 seroconversion in the susceptible partner was 3.2% (24/741) in the placebo group and 1.6% (12/743) in the valaciclovir group (p=0.060, approximate relative risk (95% CI): 0.50 (0.25, 0.99)].

The proportion of couples with asymptomatic seroconversion in the susceptible partner was 1.5% (11/741) in the placebo group and 1.3% (10/743) in the valaciclovir group (p= 0.996), approximate relative risk (95% CI): 0.91 (0.39, 2.12).

Valaciclovir was effective in reducing the risk of genital HSV-2 recurrence in source partners (the proportion of source partners with a genital HSV-2 recurrence was: placebo: 573/724, 79%; valaciclovir: 288/715, 40%), with the time to first recurrence being significantly longer in the valaciclovir group compared with the placebo group (p<0.001; hazard ratio 0.30, 95% CI 0.26, 0.35).

The incidence of the primary endpoint was higher in the female susceptible partners than in the male susceptible partners. The proportion of female susceptible partners in whom clinical evidence of first episode genital HSV-2 infection was reported was 4.1% (10/244) in the placebo group and 0.8% (2/244) in the valaciclovir group. The proportion of male susceptible partners in whom clinical evidence of first episode genital HSV-2 infection was reported was 1.2% (6/497) in the placebo group and 0.4% (2/499) in the valaciclovir group.

The safety profile of valaciclovir in this study was similar to that of placebo, and to that demonstrated previously for this dosing regimen in a similar population.

Prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation:

Three double-blind, randomised clinical studies were conducted to investigate the efficacy and safety of valaciclovir in the prophylaxis of CMV infection and disease following renal or heart transplantation. These studies included a total of 643 patients, of whom 320 received valaciclovir, 13 received aciclovir and 310 received placebo.

The primary efficacy endpoint in renal transplant studies was the development of CMV disease and the primary endpoint in the heart transplant study was the development of CMV antigenaemia. Secondary endpoints for the studies included CMV disease (heart transplant study), CMV infection, reduced acute graft rejection, fewer opportunistic bacterial or fungal infections and reduced herpes virus disease (HSV, VZV).

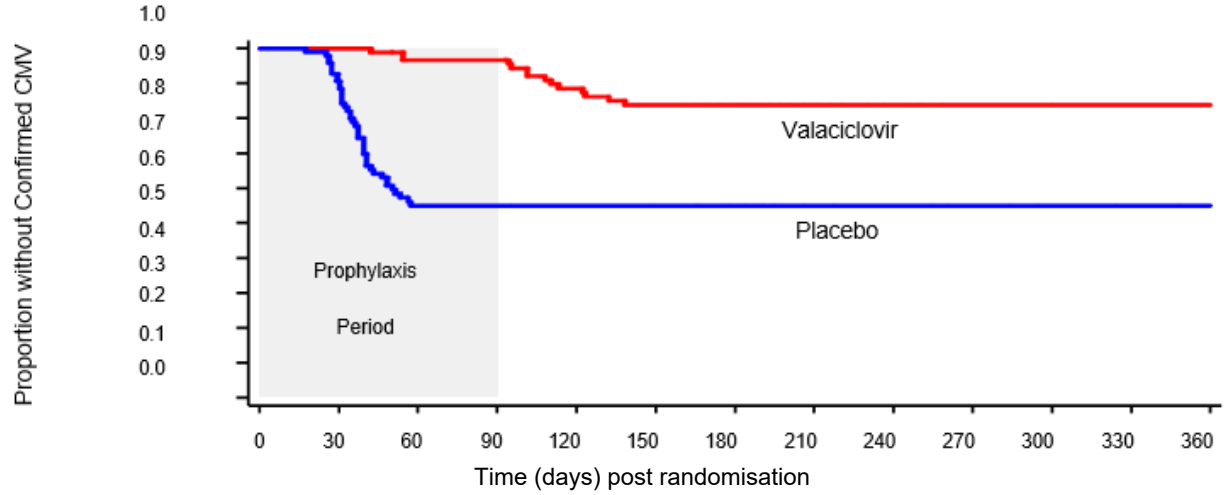
<u>Renal Transplant Studies</u>

The two renal transplant studies involved a total of 616 renal transplant recipients, of which 306

received a daily dose of 2 g valaciclovir four times daily (adjusted according to creatinine clearance for renal function) and 310 received placebo for 90 days. The patients were stratified by donor and recipient CMV-serostatus (seropositive recipients [R+] versus seronegative recipients of a graft from a seropositive donor [D+R-]). Patients commenced study drug within 72 hours post-transplant and continued treatment for 90 days (treatment period) receiving, following adjustment for renal function, a daily average dose of 4.7g ([R+] subjects) and 5.3g ([D+R-] subjects) valaciclovir. Patients were evaluated for efficacy and safety for six months post-transplant (study period).

In renal transplant recipients valaciclovir was significantly better than placebo in preventing or delaying CMV disease by 78% and 82% in the [D+R-] and [R+] strata respectively, during the six month study period. See figure below

Proportions of patients [D+R-] without confirmed CMV disease: Kaplan-Meier plots for valaciclovir versus placebo



Valaciclovir was also significantly better than placebo in preventing or delaying the development of viraemia, viruria and clinical HSV disease during the study period. No valaciclovir recipient developed VZV disease, whereas 2% and 4% of placebo patients did, R+ and D+R- strata respectively. Additionally in D+R- patients, valaciclovir was shown to significantly reduce acute graft rejections (biopsy proven and clinical acute rejection by 57% and 45% respectively) and opportunistic infections (48% primarily bacterial and fungal infections). There were no significant differences in rates of chronic graft rejection. Allograft function and survival, including the proportion of patients with a functional graft at their last assessment were similar between treatment groups. Administration of valaciclovir was associated with significantly fewer hospital admissions and reduced use of ganciclovir and aciclovir for the treatment of CMV disease or other herpes virus infections, respectively.

Heart Transplant Studies

The third study enrolled 27 heart transplant recipients. This study compared valaciclovir (n = 14, 2 g four times daily, adjusted according to creatinine clearance for renal function) with aciclovir (n = 13, 200 mg four times daily). Treatment was commenced within 3 days post-transplant and continued for 90 days. Patients were followed up until the end of the sixth month.

During the 90 day treatment period, 29% of patients on valaciclovir developed CMV antigenaemia (primary endpoint) compared to 92% of patients who received aciclovir. The time difference to CMV antigenaemia was statistically significant, with median time to CMV antigenaemia of 19 vs. 119 days in favour of valaciclovir (HR=0.422, 95%CI: 0.179, 0.992; p=0.049). At the end of the study period (3 months following the treatment period) the proportion of patients with CMV antigenaemia was similar in both treatment arms.

Notable but not statistically significant reductions in the rates of CMV infection (valaciclovir 43%, aciclovir 92%), symptomatic CMV infection (valaciclovir 0%, aciclovir 38%), CMV disease (valaciclovir 0%, aciclovir 23%) and HSV disease (valaciclovir 29%, aciclovir 54%), were observed during the 90

day treatment period. The incidence of other infections (bacterial, fungal, non-herpes virus) was also lower in the valaciclovir group throughout the entire study period (valaciclovir 36%, aciclovir 62%). There were no significant differences in graft rejection and survival rates between the valaciclovir and aciclovir patients at the end of the study (3 months following treatment period).

Results for the primary and secondary endpoints in the pivotal trials

Endpoints	Renal [D+ R-]			Renal [R+]			Heart		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
CMV disease	0.22	0.12, 0.40	< 0.0001	0.18	0.04, 0.83	<0.027	0.19	0.02, 1.70	0.09
CMV antigenaemia	n/d	n/d	n/d	n/d	n/d	n/d	0.42	0.18, 0.99	0.049
CMV infection	n/d	n/d	n/d	n/d	n/d	n/d	0.46	0.20, 1.06	0.075
CMV viraemia	0.25	0.14, 0.44	<0.0001	0.28	0.18, 0.45	<0.0001	n/d	n/d	n/d
CMV viruria	0.49	0.32, 0.76	0.001	0.32	0.24, 0.44	<0.0001	n/d	n/d	n/d
Acute graft rejection - biopsy proven - clinical	0.43 0.55	0.27, 0.70 0.37, 0.83	0.001 0.004	0.86 0.75	0.60, 1.22 0.55, 1.03	0.40 0.073	0.51 n/d	0.22, 1.19 n/d	0.09 n/d
Opportunistic infections	0.52	0.36, 0.76	0.001	0.90	0.70, 1.16	0.41	(0.42)*	NP	NP
HSV disease	0.33	0.15, 0.74	0.007	0.16	0.09, 0.30	<0.0001	n/d	n/d	n/d
VZV disease	Did not develop			Did not develop			Did not develop		

Results based on entire study period (3 months treatment followed by 3 months follow up)
* odds ratio in brackets n/d = not done NP = not protocolled

Bone marrow transplant studies

Two additional clinical studies have been conducted to assess the safety and efficacy of valaciclovir in the prophylaxis of CMV infection in bone marrow transplant recipients. The adverse event data from these trials is consistent with the current safety profile of valaciclovir.

5.2 Pharmacokinetic properties

Absorption

After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from human liver. Mean peak aciclovir concentrations are 10-37 micromoles/L (2.2-8.3 micrograms/mL) following single doses of 250-2000 mg valaciclovir to healthy subjects with normal renal function, and occur at a median time of 1.00-2.00 hours post dose. The time to peak (T_{max}) is 1.6 hours for 2 x 500 mg tablets and 1.9 hours for a 1000 mg tablet. The bioavailability of aciclovir from 1000 mg valaciclovir is 54%, and is unaffected by food. Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occur at a median time of 30 to 100 minutes post dose, and are at or below the limit of quantification 3 hours after dosing.

Aciclovir maximum concentration (C_{max}) and area under the aciclovir concentration-time curve (AUC) after single-dose administration of 100 mg, 250 mg, 500 mg, 750 mg, and 1 gram of valaciclovir to 8 healthy volunteers resulted in the mean C_{max} (± SD) of 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14), and 5.65 (± 2.37) mcg/mL, respectively; and a mean AUC (± SD) of 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11 (± 3.54), and 19.52 (± 6.04) hr•mcg/mL, respectively.

Similarly aciclovir C_{max} and AUC after the multiple-dose administration of 250 mg, 500 mg, and 1 gram of valaciclovir administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers resulted in a mean C_{max} (± SD) of 2.11 (± 0.33), 3.69 (± 0.87), and 4.96 (± 0.64) mcg/mL, respectively, and a mean AUC (± SD) of 5.66 (± 1.09), 9.88 (± 2.01), and 15.70 (± 2.27) hr•mcg/mL, respectively.

Distribution

Binding of aciclovir to plasma proteins is very low (9 to 33%). CSF penetration, determined by CSF/plasma AUC ratio, is about 25% for aciclovir and the metabolite 8-hydroxy-aciclovir (8-OH-ACV), and about 2.5% for the metabolite 9-(carboxymethoxy) methylguanine (CMMG), regardless of renal function (see section 5.2).

Biotransformation

After oral administration, valaciclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9-(carboxymethoxy) methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolised by cytochrome P450 enzymes.

Elimination

In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the known aciclovir metabolite, 9-(carboxymethoxy) methylguanine (CMMG), in the urine.

Characteristics in patients

Herpes zoster and herpes simplex do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir.

Special patient populations:

Renal impairment

The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, in severe renal impairment compared with normal renal function. There was no difference in extent of CSF penetration (as determined by CSF/plasma AUC ratio) for aciclovir, CMMG or 8-OH-aciclovir between the two populations (see section 5.2).

Hepatic impairment

Administration of valaciclovir to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valaciclovir to aciclovir is reduced, and the aciclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis. For higher doses (4000 mg or more per day) see section 4.4.

HIV infection

In patients with HIV infection, the disposition and pharmacokinetic characteristics of aciclovir after oral administration of single or multiple doses of 1000 mg or 2000 mg valaciclovir are unaltered compared with healthy subjects.

Organ transplantation

In transplant recipients receiving valaciclovir 2000 mg four times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Elderly

After single-dose administration of 1 gram of valaciclovir in healthy geriatric volunteers, the half-life of aciclovir was 3.11 ± 0.51 hours, compared with 2.54 ± 0.33 hours in healthy younger adult volunteers. The pharmacokinetics of aciclovir following single- and multiple-dose oral administration of valaciclovir in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Genotoxicity

Valaciclovir was not mutagenic in bacterial cells nor did it demonstrate any clastogenic potential *in vitro* in human lymphocytes or *in vivo* in the rat bone marrow assay. The mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg. Valaciclovir, at concentrations ≥2000 µg/mL in the presence of S9 metabolic activation was mutagenic in the mouse lymphoma assay. The active metabolite, aciclovir, was clastogenic in Chinese hamster cells *in vivo,* at exposure levels also causing nephrotoxicity (500 & 1000 mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100 mg/kg) of aciclovir in rats. No activity was found in a dominant lethal study in mice or in 4 microbial assays. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells, negative at 2 other loci in mouse lymphoma cells and 3 loci in a Chinese hamster ovary cell line).

The results of these mutagenicity tests *in vitro* and *in vivo* suggest that valaciclovir and aciclovir are unlikely to pose a genetic threat to man at therapeutic dose levels.

Fertility

Valaciclovir did not impair fertility or reproduction in rats dosed by the oral route at 200mg/kg per day, corresponding to plasma levels 2.8 (HZV) and 0.3 (CMV) times human plasma concentration (AUC). However, high parenteral doses of aciclovir caused testicular atrophy and aspermogenesis in rats (80mg/kg/day) and dogs (100mg/kg/day).

Use in lactation

Lactating rats given a 25 mg/kg PO dose of 14C-valaciclovir showed peak milk radioactivity levels of 26 mcg/eq/g, 2 hours post dose. The milk radioactivity levels declined slower than in plasma, and were undetectable at 12 hours. Suckling pups had radioactivity in the stomach and intestinal contents up to 7 hours post dose, but not in tissues.

Teratogenicity

Valaciclovir was not teratogenic in rats or rabbits given oral doses of 400 mg/kg (which results in exposures of 1.1 and 2.0 times (HSV) and 0.4 and 0.7 times (CMV) human exposure, respectively, based on body surface area) during the period of major organogenesis. Aciclovir was not teratogenic in the mouse (450 mg/kg PO), rabbit (50 mg/kg SC and IV) or rat (50 mg/kg SC) when dosed throughout the period of organogenesis. Plasma concentrations of aciclovir in the rat were 3.5 (HZV) and 0.8 (CMV) times human concentrations. In additional studies in which rats were given three SC

doses of 100 mg/kg aciclovir on gestation day 10, foetal abnormalities, such as head and tail anomalies, were reported. Plasma concentration of aciclovir in the rat were 19 (HZV) and 4.3 (CMV) times human concentration.

Mutagenicity

The results of mutagenicity tests *in vitro* and *in vivo* indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity

The data presented below include references to the steady-state aciclovir AUC observed in humans treated with 1 gram valaciclovir given orally three times a day to treat herpes zoster (HZV) or with 2 gram valaciclovir given orally four times a day to treat cytomegalovirus (CMV). Plasma drug concentration in animal studies are expressed as multiples of human exposure to aciclovir.

Valaciclovir was noncarcinogenic in lifetime carcinogenicity bioassay at oral doses of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tuours between treated and control animals, nor did valaciclovir shorten the latency of tumours. Plasma concentration (AUC) of aciclovir were equivalent to 1.1 (HZV) and 0.1 times (CMV) human levels in the mouse bioassay and 1.3 (HZV) and 0.1 (CMV) times human concentration in the rat bioassay.

6. Pharmaceutical Particulars

6.1 List of excipients

VACLOVIR tablets contain the following excipients:

- Cellulose microcrystalline
- Magnesium stearate
- Hypromellose
- Titanium dioxide
- Polyethylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

VACLOVIR 500 mg tablets are available in OPA / AL / PVC / AL cold form blister packs of 2, 4, 6, 10, 20, 30, 42, 60, 80, 90, 100, 240 & 480 tablets and HDPEB bottles of 30, 100, 240, 480 & 500 tablets.

VACLOVIR 1000 mg tablets are available in OPA / AL / PVC / AL cold form blister packs of 3, 21 & 30 tablets and HDPE bottles of 100 & 250 tablets.

Not all strengths, pack types or sizes may be marketed.

6.6 Special precautions for disposal

N/A

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

16 September 2010

10. Date of Revision of the Text

20 February 2026

Section	Summary of changes
4.4	Additional information regarding the frequency of viral shedding and the risk of transmission in the use of genital herpes.
4.5	Additional information regarding the interactions and specific consequences with other medicines like tenofovir, cimetidine, probenecid and mycophenolate mofetil.
4.6	Additional information regarding the malformative or foeto/neonatal toxicity and reproductive toxicity.
4.8	Additional information on more serious adverse effects.
4.9	Minor editorial changes.